REMARK

Applicants' representatives wish to thank Examiner Romeo for meeting on June 11, 2003, and for his many helpful suggestions and comments.

Support for the claims can be found in the specification as follows:

Claims 42-45, 50-53, 58-61: page 9, lines 13-15; page 20, lines 2-6; and page 27, line 28 to page 28, line 2.

Claims 46, 54 and 62: page 25, lines 16-24 and page 26, lines 16-22.

Claims 47, 55 and 63: page 28, line 4 to page 29, line 22.

Claims 48, 49, 56, 57, 64 and 65: page 42, line 22 to page 45, line 28 and claim 29 as originally filed.

Substance of the interview

At the interview of June 11, 2003, the utility of the invention for diagnostic purposes was discussed. Additionally, Examiner Romeo suggested appropriate claim language for claiming polypeptide fragments, and recommended amending the claims to no longer cite "pharmaceutical."

The claims have been amended accordingly. No new matter has been added. Claims 42-65 are pending.

Synopsis of case

Cancer claims over half a million individuals a year in the US alone and is the second leading cause of death (American Cancer Society, 2002). Despite the many advances in cancer research, diagnosis and therapy, much remains to be learned before this killer can be tamed.

One approach that yields not only information about cancer cells, but also tools for cancer treatment and diagnosis, is differential expression analyses in appropriate model systems. The elucidation of molecular events that correlate with cellular transformation would enable early detection, the prescription of effective treatment and provide therapeutic targets (page 2, lines 14-20; page 10, line 29 to page 11, line 11).

Oncogenes, such as *Wnt-1*, are genes that when mis-regulated are linked to cancer; these genes usually encode polypeptides that control cell growth or its regulation (page 2, lines 1-3). In the case of Wnt, family members are cysteine-rich, glycosylated signaling proteins that mediate diverse developmental processes, such as the control of cell proliferation, adhesion, cell polarity, and the establishment of cell fates (page 2, lines 1-3). Components of the Wnt signaling pathway have been linked to tumorigenesis in familial and sporadic colon carcinomas, breast cancer, and melanoma (page 2, lines 16-17).

Wnt-1 itself was shown to be an oncogene in mouse mammary tumors, but this gene was not significantly up-regulated in most human breast carcinoma cells (Nusse and Varmus, 1992; Tsukamoto *et al.*, 1988), seemingly contradicting the mouse results. The plain correlation of *Wnt-1* up-regulated expression with human breast carcinoma, however, is too simplified: molecular targets in the Wnt-1 signaling pathway are more likely to be oncogenes (Brown 2001)

The inventors have identified an important downstream cellular component of the Wnt-1 signaling pathway in mammary cells transformed by *Wnt-1*, solving the problem of the identification of down-stream Wnt-1 targets. Such a molecule is useful in the diagnosis and treatment of carcinomas, such as breast carcinomas. For example, antibodies that specifically bind these polypeptides can be used as diagnostic markers (page 10, lines 29 to page 11, line 11; page 56, line 2 to page 57, line 18).

To elucidate the genes that are differentially regulated in cancers that arise due to malfunctions in the Wnt-signaling pathway, tumors that spontaneously arise in transgenic mice over-expressing *Wnt-1* at 1-5 months after parturition were examined for differential gene expression when compared to wild-type age-matched mice mammary glands (page 87, line 30 to page 88, line 2). In the absence of *Wnt-1* control, unregulated genes that play crucial roles in the cell transformation processes are evidenced in the spontaneously arising tumors. For example, disruption of the canonical pathway (β-catenin cytosolic stability) is a major feature of neoplasia (page 1, lines 24-27). Genes that are expressed at levels that differ significantly from wild-type tissues are *Wnt-1* signaling pathway candidates and represent diagnostic and therapeutic targets for neoplasias.

mRNA was isolated from both the tumor and wild-type tissues and subjected to Quantitative Expression Analysis (QEA) (page 88, lines 3-6). Those fragments that were differentially expressed were then queried according to the Gene Calling technology (page 88, lines 5-6) to identify full length sequences.

The results of these experiments identified the polynucleotide fragment, SEQ ID NO:1, from which SEQ ID NO:2 was assembled. SEQ ID NO:2 encodes the polypeptide of SEQ ID NO:3. Using the mouse polynucleotide sequence (SEQ ID NO:1), a human expressed sequence tag (EST), SEQ ID NO:4, was identified. This EST was identified in human cells that form a metastatic tumor when implanted in mice (page 8, lines 14-15). Using Gene Calling, SEQ ID NO:5 was assembled, representing the human homologue of SEQ ID NO:2. SEQ ID NO:5 encodes the polypeptide SEQ ID NO:6. A summary of the devolution of these sequences is shown in **Table 1** (*see also* page 6, line 24 to page 9, line 15 and page 88, line 7 to page 89, line 2).

Table 1 Relationship of sequences with each other

SEQ ID NO:	Provenance and description
1	mouse; used as "probe" to assemble SEQ ID NO:2
2	mouse; sequence of S100 cytokine-like molecule
3	mouse; polypeptide encoded by SEQ ID NO:3
4	human; identified by using SEQ ID NO:1 as a "probe"
5	human; sequence of S100 cytokine-like molecule
6	human; polypeptide encoded by SEQ ID NO:6

To confirm the role that SEQ ID NOs:5 and 6 have in tumors, the expression of SEQ ID NO:5 was used to probe a broad array of tissues and cell lines (page 89, line 4 to page 92, line 9). Tissues that were probed included pancreas, thyroid; adrenal, salivary and pituitary glands; brain, spinal cord, heart, skeletal muscle, bone marrow, thymus, spleen, rectal, stomach, small intestine, liver, lung, mammary gland, ovary, uterus, placenta, and prostate. Cells that were probed included those derived from carcinomas, such as renal, central nervous system, colon, lung ovarian, prostate, colon, gastric and melanoma carcinomas. SEQ ID NO:5 is strongly and differentially expressed in colon, breast and ovarian tumor cells as compared to the wild-type counterparts (Table 8, pages 90-92; page 92, lines 4-6).

These results indicate that SEQ ID NO:5 and its counterparts, SEQ ID NOs:1-4 and 6, are useful for cancer diagnostic tests (*e.g.*, for SEQ ID NO:5, *see* page 92, lines 6-7). Such tests can not only be used for the detection of colon, breast and ovarian cancers, but also can be used to assess treatment efficacy after cancer detection. Thus SEQ ID NO:3, the polypeptide of the

claimed invention, can be used to generate antibodies (page 10, line 29 to page 11, line 11; page 56, line 14 to page 57, line 2), and the antibody used to probe biopsy samples or isolated cells from a subject.

Rejections under 35 USC § 101

The rejections of the claims under 35 USC § 101 are respectfully traversed. The diagnostic utility of the claimed invention is specific, substantial, and credible.

The utility of the claimed invention is specific for the detection of colon, breast and ovarian cancers. Not only was SEQ ID NO:3 identified in an art-accepted model for cancer (Tsukamoto *et al.*, 1988; Wong *et al.*, 1994), shown to be up-regulated in spontaneously arising tumor cells, but expression analysis shows that its expression, as evidenced by its human homologue (SEQ ID NO:5, encoding SEQ ID NO:6), is restricted to a few tissues, and is greatly up-regulated in colon, breast and ovarian cancer cells (Table 8, pages 90-92; page 92, lines 4-6). Antibodies generated to the polypeptide of SEQ ID NO:3 can be used to specifically detect colon, breast and ovarian cancer cells.

The utility of the claimed invention is substantial. Ovarian cancer alone claims the lives of 14,000 woman annually in the U.S. (Mayo Clinic, 2003). Given the unreliability of testing for the only available marker, CA 125 (only tested for in survivors of ovarian cancer for detection of recurrence; Mayo Clinic, 2003), having additional antigens will allow for more sure and earlier detection, as well as brighter prospects for those afflicted because early interventions are more likely to succeed.

The utility of the claimed invention is credible for detecting the presence of colon, breast and ovarian cancer cells. As shown by the results in Table 8 (pages 90-92), the polynucleotide encoding the human homologue of SEQ ID NO:3 is highly up-regulated only in a few cancer cell types, but not in the tested wild-type tissues. The up-regulation being restricted to a few cancer cell types indicates that using the polypeptide of SEQ ID NO:3 as a tool to diagnose cancer is credible.

Because the claimed invention has a specific, substantial and credible diagnostic utility, the rejections under 35 USC § 101 and related rejections under 35 USC § 112, first paragraph, are respectfully requested to be withdrawn.

Rejections under 35 USC § 112, first paragraph

Additional rejections of the claims under 35 USC § 112, first paragraph (page 8, line 14 to page 9, line 11 of paper no. 17) have been obviated by amendment. Applicants now specifically claim the sequence of SEQ ID NO:3 as identified on page 9, Table 6 of the specification. Furthermore, the added functional limitations further obviate the rejections (page 9, line 11 to page 12, line 14 of paper no. 17). As was suggested during the interview, for other claims, because the human sequence is presented in the application (SEQ ID NO:6), this sequence provides guidance for modifying the claimed mouse sequence, SEQ ID NO:3, without losing function. Sequence identity was calculated from comparing the mouse sequence of the instant invention with that of the human using BLAST; between them, 86% sequence identity was found. Because of the close relationship of these polypeptides as evidenced by the high sequence identity, the polypeptides should be functionally similar.

Rejections of the claims that formerly cited "pharmaceutical" have been obviated by appropriate amendment; other objectionable claim language has also been appropriately amended.

Rejections under 35 USC § 102(b)

Rejection of the claims under 35 USC § 102(b) has been obviated by amendment.

Other cited references

American Cancer Society. (2002) *Cancer Facts and Figures*. Atlanta, GA: American Cancer Society, Inc..

Brown, A.M. (2001) Wnt signaling in breast cancer: have we come full circle? *Breast Cancer Res* 3, 351-355.

Mayo Clinic online publication. 2003. Ovarian cancer.

Nusse, R. and Varmus, H.E. (1992) Wnt genes. *Cell* 69, 1073-1087.

Tsukamoto, A.S., Grosschedl, R., Guzman, R.C., Parslow, T. and Varmus, H.E. (1988) Expression of the int-1 gene in transgenic mice is associated with mammary gland hyperplasia and adenocarcinomas in male and female mice. *Cell* 55, 619-625.1.

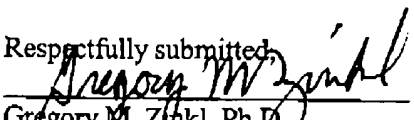
Wong, G.T., B.J. Gavin, and A.P. McMahon. 1994. Differential transformation of mammary epithelial cells by Wnt genes. *Mol. Cell. Biol.* 14:6278-6286.

CONCLUSION AND REQUEST FOR RECONSIDERATION

Reconsideration and withdrawal of all claim rejections is respectfully requested. Applicants believe that all claims in the present application are in condition for allowance.

Should the Examiner have any questions, or would like to discuss any matters in connection with the present application, the Examiner is invited to contact the undersigned at (312) 876-8936.

Respectfully submitted,



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